

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING APPLICATION

Under Rule 53(a), (b)(1) & (d)(1)

(No Filing Fee or Oath/Declaration)

(Do NOT use for Provisional or PCT Applications)

Use for Design or Utility Applications

PATENT
APPLICATION

RULE 53(d) NO DECLARATION

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Atty. Dkt.

241249

M#

96/09PH

Client Ref

Date:

MONDAY, September 8, 1997

Sir:

1. This is a Request for filing a new Patent Application (☐ Design ☒ Utility) entitled:

2. (Complete) Title: N-substituted indole-3-glyoxylamides having anti-asthmatic, antiallergic and immunosuppressant/immuno-modulating action
without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).4. 35 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language6. 8 Numbered claim(s); and

7. ☐ sheet(s) per set: ☐ 1 set informal; 8. ☐ formal of size: ☐ A4 ☐ 11"
 Drawings:

9. DOMESTIC/INTERNATIONAL priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

10. FOREIGN priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in GERMANY

Application No.	Filing Date	Application No.	Filing Date
(1)	19636150.8	(2)	
(3)		(4)	
(5)		(6)	

11. 1 (No.) Certified copy (copies): ☒ attached; ☐ previously filed (date)
 in U.S. Application No. / filed on

12. ☐ This is a reissue of Patent No.

13. ☐ **Amend the specification** by inserting before the first line - This is a ☐ Continuation-in-Part
☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

13(a) ☐ National Appln. No. / filed -- (M#)

13(b) ☐ International Appln. No. PCT/ filed which
 designated the U.S. --

14. ☐ See top of first page re continuing appln (X box only if info is there)14(a) extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

15. ☐ Prior application is assigned to

by Assignment recorded _____ Reel _____ Frame _____

16. [X] Attached:

Translation verification certificate

17. This application is made by the following named inventor(s) (Double check instructions for accuracy):

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18. NOTE: FOR ADDITIONAL INVENTORS, check box ☒
and attach sheet with same information regarding additional inventors.

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NOTE: File in duplicate with 2 post card receipts (CDC-103) & attachments

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b)(1) & (d)(1)
(Continued : Additional Inventors)

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APPLICATION UNDER UNITED STATES PATENT LAWS

Invention: N-substituted indole-3-glyoxylamides having anti-asthmatic, antiallergic and immunosuppressant/immuno-modulating action

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This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
Filed _____

SPECIFICATION

N-substituted / having anti-asthmatic, antiallergic and immunosuppressant/immuno-modulating action

Description

5

Indole-3-glyoxylamides have various uses as pharmacodynamically active compounds and as synthesis components in the pharmaceutical chemistry.

- 10 The Patent Application NL 6502481 describes compounds which have an antiinflammatory and antipyretic profile of action and analgesic activity.

- The British Patent GB 1 028 812 mentions derivatives of
15 indolyl-3-glyoxylic acid and its amides as compounds having analgesic, anticonvulsant and β -adrenergic activity.

- G. Domschke et al. (Ber. 94, 2353 (1961)) describe 3-
20 indolylglyoxylamides which are not characterized pharmacologically.

- E. Walton et al. in J. Med. Chem. 11,1252 (1968) report on indolyl-3-glyoxylic acid derivatives which have an
25 inhibitory activity on glycerophosphate dehydrogenase and lactate dehydrogenase.

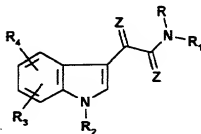
- European Patent Specification EP 0 675 110 A1 describes 1H-indole-3-glyoxylamides which are profiled
30 as sPLA2 inhibitors and are used in the treatment of septic shock, in pancreatitis, and in the treatment of allergic rhinitis and rheumatoid arthritis.

- The aim of the present invention is to make available
35 novel compounds from the indolyl-3-glyoxylic acid series, which have antiasthmatic and immunomodulating action.

- The chemical processes for the preparation of these
40 compounds and pharmaceutical processes for the con-

version of the novel compounds into medicaments and their preparation forms are furthermore described.

The subject matter of the invention comprises compounds of the general formula I,

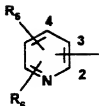


Formula I

where the radicals R, R₁, R₂, R₃, R₄ and Z have the following meaning:

R = hydrogen, (C₁-C₆)-alkyl, where the alkyl group can be mono- or polysubstituted by the phenyl ring. This phenyl ring, for its part, can be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, by carboxyl groups, carboxyl groups esterified with (C₁-C₆)-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups, benzyloxy groups and by a benzyl group which is mono- or polysubstituted in the phenyl moiety by (C₁-C₆)-alkyl groups halogen atoms or trifluoromethyl groups.

R₁ can be a phenyl ring which is mono- or polysubstituted by (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, hydroxyl, benzyloxy, nitro, amino, (C₁-C₆)-alkylamino, (C₁-C₆)-alkoxy-carbonylamino and by a carboxyl group or a carboxyl group esterified by (C₁-C₆)-alkanols, or is a pyridin structure of the formula II



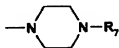
Formula II

where the pyridin structure is alternatively bonded to the ring carbon atoms 2, 3 and 4 and can be substituted by the substituents R_5 and R_6 . The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6) -alkyl, and also the meaning (C_3-C_7) -cycloalkyl, (C_1-C_6) -alkoxy, nitro, amino, hydroxyl, halogen and trifluoromethyl and are furthermore the ethoxy-carbonylamino radical and the group carboxy-alkyloxy in which the alkyl group can have 1-4 C atoms.

R_1 can furthermore be a 2- or 4-pyrimidinyl-heterocycle or a pyridylmethyl radical in which CH_2 can be in the 2-, 3-, 4-position where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group, furthermore are [sic] the 2-, 3- and 4-quinolyl structure substituted by (C_1-C_6) -alkyl, halogen, the nitro group, the amino group and the (C_1-C_6) -alkylamino radical, or are [sic] a 2-, 3- and 4-quinolylmethyl group, where the ring carbons of the pyridylmethyl and quinolylmethyl radical can be substituted by (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, nitro, amino and (C_1-C_6) -alkoxy-carbonylamino.

R_1 for the case where R is hydrogen or the benzyl group, can furthermore be the acid radical of a natural or unnatural amino acid, e.g. the α -glycyl, the α -sarcosyl, the α -alanyl, the α -leucyl, the α -isoleucyl, the α -seryl, the α -phenylalanyl, the α -histidyl, the α -prolyl, the

5 α -arginyl, the α -lysyl, the α -asparagyl and the
 α -glutamyl radical, where the amino groups of the
 respective amino acids can be present in
 unprotected or protected form. Possible
 protective groups for the amino function are the
 carbobenzoxy radical (Z radical) and the tert-
 butoxycarbonyl radical (BOC radical) and also the
 acetyl group. In the case of the asparagyl and
 10 glutamyl radical claimed for R_1 , the second,
 nonbonded carboxyl group is present as a free
 carboxyl group or in the form of an ester with
 C_1 - C_6 -alkanols, e.g. as the methyl, ethyl or as
 the tert-butyl ester. R_1 can furthermore be the
 allylaminocarbonyl-2-methylprop-1-yl group. R and
 15 R_1 , together with the nitrogen atom to which they
 are bonded, can furthermore form a piperazine
 ring of the formula III or a homopiperazine ring
 if R_1 is an aminoalkylene group in which



20 Formula III

25 R_1 is an alkyl radical, a phenyl ring which can be
 mono- or polysubstituted by (C_1-C_6) -alkyl, (C_1-C_6) -
 alkoxy, halogen, the nitro group, the amino
 function, by (C_1-C_6) -alkylamino, the benzhydryl
 group and the bis-p-fluorobenzylhydryl group.

30 R_2 can be hydrogen or the (C_1-C_6) -alkyl group, where
 the alkyl group can be mono- or polysubstituted by
 halogen and phenyl which for its part can be mono-
 or polysubstituted by halogen, (C_1-C_6) -alkyl, $(C_3$ -
 $C_7)$ -cycloalkyl, carboxyl groups, carboxyl groups
 esterified with (C_1-C_6) -alkanols, trifluoromethyl
 groups, hydroxyl groups, methoxy groups, ethoxy
 35 groups or benzyloxy groups. The (C_1-C_6) -alkyl group
 counting as R_2 can furthermore be substituted by
 the 2-quinolyl group and the 2-, 3- and 4-pyridyl

structure, which in each case can both be mono- or polysubstituted by halogen, (C₁-C₄)-alkyl groups or (C₁-C₆)-alkoxy groups. R₂ is furthermore the aroyl radical, where the aroyl moiety on which this radical is based is the phenyl ring which can be mono- or polysubstituted by halogen (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, carboxyl groups, carboxyl groups esterified by (C₁-C₆)-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups.

R₃ and R₄ can be identical or different and are hydrogen, hydroxyl, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkanoyl, (C₁-C₆)-alkoxy, halogen and benzyloxy. R₃ and R₄ can furthermore be the nitro group, the amino group, the (C₁-C₄)-mono- or dialkyl-substituted amino group, and the (C₁-C₃)-alkoxycarbonylamino function or (C₁-C₃)-alkoxy-carbonylamino- (C₁-C₃)-alkyl function.

Z is O or S

The designation alkyl, alcohol, alkoxy or alkylamino group for the radicals R, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is normally to be understood as meaning "straight-chain" and "branched" alkyl groups, where "straight-chain alkyl groups" can be, for example, radicals such as methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl and "branched alkyl groups" designate, for example, radicals such as isopropyl or tert-butyl. "Cycloalkyl" is to be understood as meaning radicals such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The designation "halogen" represents fluorine, chlorine, bromine or iodine. The designation "alkoxy group" represents radicals such as, for example, methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or pentoxy.

The compounds according to the invention can also be present as acid addition salts, for example as salts of mineral acids, such as, for example, hydrochloric acid, sulfuric acid, phosphoric acid, salts of organic acids, such as, for example, acetic acid, lactic acid, malonic acid, maleic acid, fumaric acid, gluconic acid, glucuronic acid, citric acid, embonic acid, methanesulfonic acid, trifluoroacetic acid and succinic acid.

10

Both the compounds of the formula I and their salts are biologically active. The compounds of the formula I can be administered in free form or as salts with a physiologically tolerable acid.

15 Administration can be carried out orally, parenterally, intravenously, transdermally or by inhalation.

The invention furthermore relates to pharmaceutical preparations containing at least one compound of the formula I or its salt with physiologically tolerable inorganic or organic acids and, if appropriate, pharmaceutically utilizable excipients and/or diluents or auxiliaries.

20

25 Suitable administration forms are, for example, tablets, coated tablets, capsules, solutions or ampoules, suppositories, patches, powder preparations which can be inhaled, suspensions, creams and ointments.

30

The compounds according to the invention have a good antiasthmatic, antiallergic and immuno-suppressant/immunomodulating action, for example in transplantations and diseases such as psoriasis, 35 rheumatoid disorders and chronic polyarthritis, in the following pharmacological models:

**Inhibition of the "late phase" eosinophilia in the BAL
24 hours after allergen challenge in guinea pigs**

Male guinea pigs (200 - 250 g, Dunkin Hartley Shoe)
5 were actively sensitized subcutaneously with ovalbumin
(10 µg of ovalbumin + 1 mg of Al(OH)₃) and boosted 2
weeks later. One week after boosting with ovalbumin,
the animals were exposed to an inhalation challenge
with ovalbumin (0.5 % strength solution) for 20 - 30
10 seconds. 24 hours later, the animals were killed by
means of an overdose of urethane, exsanguinated and a
bronchoalveolar lavage (BAL) was carried out using 2 x
5 ml of 0.9 % strength physiological saline solution.

15 The lavage fluid was collected and centrifuged at 400 g
for 10 minutes, and the pellets were suspended in 1 ml
of 0.9 % strength physiological saline solution. The
eosinophils were counted microscopically in a Neubauer
chamber after staining by means of Becton Dickinson
20 test kit No. 5877. This test kit contains Phloxin B as
a selective stain for eosinophils. The eosinophils in
the BAL was [sic] counted here for each animal and
expressed as eosinophils (millions/animal). For each
group the mean value and standard deviation were
25 determined. The percentage inhibition of eosinophilia
for the group treated with test substance was
calculated according to the following formula:

$$(A - B) - (B - C) / (A - C) \times 100 = \% \text{ inhibition}$$

30 in this formula A eosinophils correspond to the
untreated challenge group, B eosinophils to the treated
group and C eosinophils to the unchallenged control
group.

35 The animals were treated with a histamine H₁ antagonist
(azelastine; 0.01 mg/kg p.o.) 2 hours before allergen
challenge to avoid death. The administration of the
test substances or of the vehicle was carried out 4

hours after allergen challenge. The percentage inhibition of eosinophilia in the BAL was calculated on groups of 6 - 10 animals.

5 Table: Inhibition of the "late phase" - eosinophilia
24 h after allergen challenge in guinea pigs

Substance	Dose [mg/kg]	Administration	n	% Inhibition
Cyclosporin A	5	i.p. + 4h	17	50.0
	10	i.p. + 4h	11	47.0
	30	p.o. + 4h	10	68.8
According to Ex. 1	5	i.p. + 4h	10	27.8
	10	i.p. + 4h	10	55.4
	30	p.o. + 4h	9	56.1

10 Assays for the determination of peptidylprolyl
isomerase (PPIase) activity and inhibition

The PPIase activity of the cyclophilins was measured enzymatically according to Fischer et al. (1984). After isomerization of the substrate by the peptidyl prolyl isomerase, this is accessible to chymotrypsin, which cleaves the chromophore p-nitroaniline. For the determination of inhibition of the PPIase activity by substance, recombinant human Cyp B was used. The interaction of Cyp B with a potential inhibitor was carried out as follows:

A certain concentration of purified Cyp B was incubated with 1 μ M substance for 15 min. The PPIase reaction was started by addition of the substrate solution to the reaction mixture which contains HEPES buffer, chymotrypsin and either test or control samples. Under these conditions, first-order kinetics were obtained with a constant $K_{\text{observed}} = K_0 + K_{\text{enz}}$, where K_0 is the spontaneous isomerization and K_{enz} is the rate of isomerization of the PPIase activity. The extinction values which correspond to the amount of the chromophore cleaved were measured using a Beckman DU 70

spectrophotometer at a constant reaction temperature of 10 °C.

- The observed residual activity in the presence of various substances was compared with the cyclophilins only treated with solvent. The results were given in % residual activity. Cyclosporin A (CsA) was used as the reference compound. The inhibition of the PPIase activity was additionally checked by SDS-PAGE.

10 **Colorimetric assay (based on the MTT test) for the non-radioactive quantification of cell proliferation and survival ability**

MTT is used for the quantitative determination of cell proliferation and activation, for example, in the reaction on growth factors and cytokines such as IL-2 and IL-4 and also for the quantification of the antiproliferative or toxic effects.

- 20 The assay is based on the cleavage of yellow tetrazolium salt MTT to give purple-red formazan crystals by metabolically active cells.

The cells, cultured in a 96-hole tissue culture plate, are incubated for about 4 h with yellow MTT solution. After this incubation time, purple-red formazan salt crystals are formed. These salt crystals are insoluble in aqueous solutions, but can be dissolved by addition of solubilizer and by incubation of the plates overnight.

The dissolved formazan product is quantified spectrophotometrically using an ELISA reader. An increase in the number of living cells results in an increase in the total metabolic activity in the sample. This increase correlates directly with the amount of the purple-red formazan crystals formed, which are [sic] measured by the absorption.

Substance	Inhibition of PPIase activity [%]	Inhibition of CD3-induced IL-2 production [%]			Inhibition of lympho- proliferation [%]		
Conc. [μ M]		0.1	1	10	0.1	1	10
According to Ex. 1	80 - 100	34	72	95	18	39	61
Cyclosporin A	80 - 100	56	82	94	8	7	11

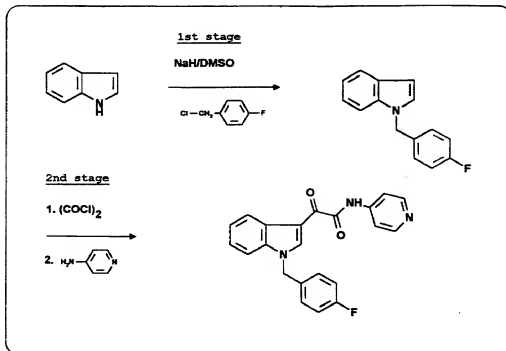
The processes for the preparation of the compounds according to the invention are described in the following reaction schemes 1 and 2 and in general procedures. All compounds can be prepared as described or analogously.

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The compounds of the general formula I are obtainable according to the following Scheme 1, shown for the synthesis of the compound Example 1:

5

Scheme 1



General procedure for the preparation of the compounds of the general formula I according to Scheme 1:

10

1st stage:

The indole derivative, which can be unsubstituted or mono- or polysubstituted on C-2 or in the phenyl structure, is dissolved in a protic, dipolar aprotic or nonpolar organic solvent, such as, for example, isopropanol, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dioxane, toluene or methylene chloride and added dropwise to a suspension of a base in a molar or excess amount prepared in a 3-necked flask under an N_2 atmosphere, such as, for example, sodium hydride, powdered potassium hydroxide, potassium tert-butoxide,

15
20

dimethylaminopyridine or sodium amide in a suitable solvent. The desired alkyl, aralkyl or heteroaralkyl halide, if appropriate with addition of a catalyst, such as, for example, copper, is then added and the mixture is reacted for some time, for example 30 minutes to 12 hours, and the temperature is kept within a range from 0°C to 120°C, preferably between 30°C to [sic] 80°C, particularly between 50°C and 65°C. After completion of the reaction, the reaction mixture is added to water, the solution is extracted, for example, with diethyl ether, dichloromethane, chloroform, methyl tert-butyl ether or tetrahydrofuran and the organic phase obtained in each case is dried using anhydrous sodium sulfate. The organic phase is concentrated in vacuo, the residue which remains is crystallized by trituration or the oily residue is purified by recrystallization, distillation or by column or flash chromatography on silica gel or alumina. The eluent used is, for example, a mixture of dichloromethane and diethyl ether in the ratio 8:2 (vol/vol) or a mixture of dichloromethane and ethanol in the ratio 9:1 (vol/vol).

2nd stage

The N-substituted indole obtained by the abovementioned 1st stage procedure is dissolved under a nitrogen atmosphere in an aprotic or nonpolar organic solvent, such as, for example, diethyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane, toluene, xylene, methylene chloride or chloroform and added to a solution, prepared under a nitrogen atmosphere, of a simply molar up to 60 percent excess amount of oxalyl chloride in an aprotic or nonpolar solvent, such as, for example, in diethyl ether, methyl tert-butylether, tetrahydrofuran, dioxane, toluene, xylene, methylene chloride or chloroform, the temperature being kept between -5°C and 20°C. The reaction solution is then heated at a temperature between 10°C and 130°C,

- preferably between 20°C and 80°C, particularly between 30°C and 50°C, for a period of 30 minutes up to 5 hours and the solvent is then evaporated. The residue of the "indolyl-3-glyoxylic acid chloride" formed in this
- 5 manner which remains is dissolved in an aprotic solvent such as, for example, tetrahydrofuran, dioxane, diethyl ether, toluene or alternatively in a dipolar aprotic solvent, such as, for example, dimethylformamide, dimethylacetamide or dimethyl sulfoxide, cooled to a
- 10 temperature between 10°C and -15°C, preferably between -5°C and 0°C, and treated in the presence of an acid scavenger with a solution of the primary or secondary amine in a diluent.
- 15 Possible diluents are the solvents used above for the dissolution of the indolyl-3-glyoxylic acid chloride. Acid scavengers used are triethylamine, pyridin, dimethylaminopyridine, basic ion exchanger, sodium carbonate, potassium carbonate, powdered potassium
- 20 hydroxide and excess primary or secondary amine employed for the reaction. The reaction takes place at a temperature from 0°C to 120°C, preferably at 20 - 80°C, particularly between 40°C and 60°C. After a reaction time of 1 - 3 hours and standing at room
- 25 temperature for 24 hours, the hydrochloride of the acid scavenger is filtered, the filtrate is concentrated in vacuo, and the residue is recrystallized from an organic solvent or purified by column chromatography on silica gel or alumina. The eluent used is, for example,
- 30 a mixture of dichloromethane and ethanol (95:5, vol/vol).

Working Examples

- 35 According to this general procedure for Stages 1 and 2, on which the synthesis Scheme 1 is based, the following compounds were synthesized which are evident from the following survey detailing the respective chemical name. In Table 1 which follows, the structures of these

compounds and their melting points can be seen from the general formula I and the substituents R_1 - R_4 and Z:

Example 1

5

N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl]
glyoxylamide

1st stage

10

1-(4-Fluorobenzyl)indole

209900-91252-00
A solution of 11.72 g (0.1 mol) of indole in 50 ml of dimethyl sulfoxide is added to a mixture of 2.64 g of sodium hydride (0.11 mol, mineral oil suspension) in 100 ml of dimethyl sulfoxide. The mixture is heated for 1.5 hours at 60°C, then allowed to cool and 15.9 g (0.11 mol) of 4-fluorobenzyl chloride are added dropwise. The solution is warmed to 60°C, allowed to stand overnight and then poured into 400 ml of water with stirring. The mixture is extracted several times with a total of 150 ml of methylene chloride, the organic phase is dried using anhydrous sodium sulfate and filtered, and the filtrate is concentrated in vacuo. The residue is distilled in a high vacuum: 21.0 g (96% of theory) B.p. (0.5 mm): 140°C

2nd stage

30

N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl]
glyoxylamide

A solution of 4.75 g (21.1 mmol) of 1-(4-fluorobenzyl)indole in 25 ml of ether is added dropwise at 0°C and under N_2 to a solution of 2.25 ml of oxalyl chloride in 25 ml of ether. The mixture is refluxed for 2 hours and the solvent is then evaporated. 50 ml of tetrahydrofuran were [sic] then added to the residue,

and the solution is cooled to -5°C and treated dropwise with a solution of 4.66 g (49.5 mmol) of 4-aminopyridine in 200 ml of THF. The mixture is refluxed for 3 hours and allowed to stand at room temperature overnight. The 4-aminopyridine hydrochloride is filtered off with suction, the precipitate is washed with THF, the filtrate is concentrated in vacuo and the residue is recrystallized from ethyl acetate.

10 Yield: 7.09 g (90% of theory)

Melting point: 225-226°C

Elemental analysis:

15	Calc.	C	70.77	H	4.32	N	11.25
	Found	C	71.09	H	4.36	N	11.26

	Example 2	N-(Pyridin-4-yl)-(1-methylindol-3-yl)glyoxylamide
	Example 3	N-(Pyridin-3-yl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
20	Example 4	N-(Pyridin-3-yl)-(1-benzylindol-3-yl)glyoxylamide
	Example 5	N-(Pyridin-3-yl)-[1-(2-chlorobenzyl)-indol-3-yl]glyoxylamide
25	Example 6	N-(4-Fluorophenyl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
	Example 7	N-(4-Nitrophenyl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
	Example 8	N-(2-Chloropyridin-3-yl)-[1-(4-fluorobenzyl)indol-3-yl]glyoxylamide
30	Example 9	N-(Pyridin-4-yl)-(1-benzylindol-3-yl)glyoxylamide
	Example 10	N-(Pyridin-4-yl)-[1-(3-pyridylmethyl)-indol-3-yl]glyoxylamide
35	Example 11	N-(4-Fluorophenyl)-[1-(2-pyridylmethyl)-indol-3-yl]glyoxylamide

- | | |
|---------------|---|
| Example 12 | N-4 (Fluorophenyl) - [1- (3-pyridylmethyl) - indol-3-yl]glyoxylamide |
| Example 13 | N- (Pyridin-4-yl) - [1- (4-chlorobenzyl) - indol-3-yl]glyoxylamide |
| 5 Example 14 | N- (Pyridin-4-yl) - [1- (2-chlorobenzyl) - indol-3-yl]glyoxylamide |
| Example 15 | N- (Pyridin-2-yl) - [1-4-fluorobenzyl) - indol-3-yl]glyoxylamide |
| Example 16 | N- (Pyridin-4-yl) - [1- (2-pyridylmethyl) - indol-3-yl]glyoxylamide |
| 10 Example 17 | (4-Phenylpiperazin-1-yl) - [1- (4-fluorobenzyl) indol-3-yl]glyoxylamide |
| Example 18 | N- (Pyridin-2-yl) - (1-benzylindol-3-yl) - glyoxylamide |
| 15 Example 19 | N- (Pyridin-4-yl) - [1- (4-fluorobenzyl) -6-ethoxycarbonylaminoindol-3-yl] - glyoxylamide |
| Example 20 | N- (Pyridin-4-yl) - [1- (4-fluorobenzyl) -5-ethoxycarbonylaminoindol-3-yl] - glyoxylamide |
| 20 Example 21 | N- (Pyridin-4-yl) - [1- (4-fluorobenzyl) -6-cyclopentyloxycarbonylaminoindol-3-yl] - glyoxylamide |
| Example 22 | 4- (Pyridin-4-yl) -piperazin-1-yl) - [1- (4-fluorobenzyl) indol-3-yl] - glyoxylamide |
| 25 Example 23 | N- (3,4,5-Trimethoxybenzyl) -N- (allylaminocarbonyl-2-methylprop-1-yl) - [1- (4-fluorobenzyl) indol-3-yl]glyoxylamide |
| Example 24 | N- (Pyridin-4-yl) - [1- (4-fluorobenzyl) -5-methoxyindol-3-yl]glyoxylamide |
| 30 Example 25 | N- (Pyridin-4-yl) - [1- (4-fluorobenzyl) -5-hydroxyindol-3-yl]glyoxylamide |
| Example 26 | N-pyridin-4-yl- [1- (4-fluorobenzyl) -5-ethoxycarbonylaminomethylindol-3-yl] - glyoxylamide |
| 35 | |

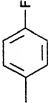
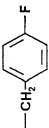
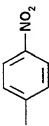
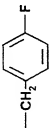

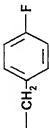




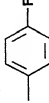

Example	R	R ₁	R ₂	R ₃	R ₄	Z	M.p.
Ex. 6	H			H	H	O	199°C
Ex. 7	H			H	H	O	>250°C
Ex. 8	H			H	H	O	149°C
Ex. 9	H			H	H	O	178-180°C
Ex. 10	H			H	H	O	179°C
Ex. 11	H			H	H	O	132°C

Table 1: Novel indolylglyoxylamides according to reaction Scheme 1

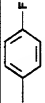








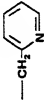



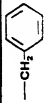
Example	R	R ₁	R ₂	R ₃	R ₄	Z	M.p.
Ex. 12	H			H	H	O	144°C
Ex. 13	H			H	H	O	234°C
Ex. 14	H			H	H	O	184°C
Ex. 15	H			H	H	O	141°C
Ex. 16	H			H	H	O	202°C
Ex. 17	R+R ₁ zusam.			H	H	O	116°C
Ex. 18	H			H	H	O	112-3°C

Table 1: Novel indolyglyoxyamides according to reaction Scheme 1



















Example	R	R ₁	R ₂	R ₃	R ₄	Z	M.P.
Ex. 19	H			6-NHCOOEt	H	O	>260°C
Ex. 20	H			6-NHCOOEt	H	O	183°C
Ex. 21	H			6-NHCOO- 	H	O	Ölig
Ex. 22	R+R ₁ zusam.			H	H	O	160-82°C
Ex. 23				H	H	O	138-141°C
Ex. 24	H			6-OCH ₃	H	O	188°C
Ex. 25	H			6-OH	H	O	>260°C
Ex. 26	H			6-CH ₂ -NHCOOEt	H	O	178-178°C

Table 1: Novel indolyglycolamides according to reaction Scheme 1

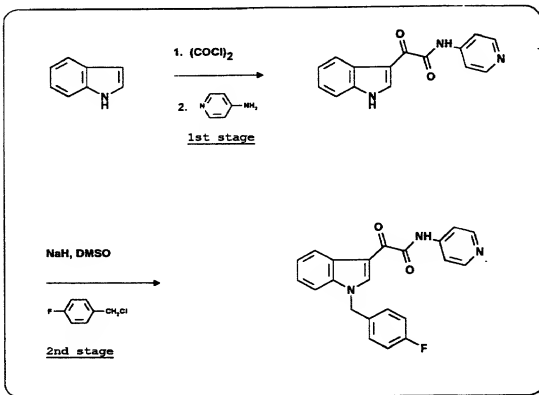
Starting materials for the compounds of the general formula 1 prepared according to synthesis Scheme 1, which come from Table 1

- 5 All precursors for the final synthesis stages of Examples 1 to 22 and 24 to 26 are commercially available.

Furthermore, the compounds of the general formula I are also obtainable according to the synthesis route of Scheme 2, shown by the synthesis of the compound Example 27:

Scheme 2

15



General procedure for the preparation of the compounds
of the general formula 1 according to Scheme 2

1st stage:

5 The indole derivative dissolved in a solvent, such as
given above for oxalyl chloride, which can be
unsubstituted or substituted on C-2 or in the phenyl
ring, is added dropwise at a temperature between -5°C
10 and +5°C to a solution of a simply molar up to 60%
excess amount of oxalyl chloride prepared under a
nitrogen atmosphere in an aprotic or nonpolar solvent,
such as, for example, in diethyl ether, methyl tert-
butyl ether, tetrahydrofuran, dioxane or alternatively
15 dichloromethane. The reaction solution is then heated
for 1 to 5 hours to a temperature between 10°C and
120°C, preferably between 20°C and 80°C, particularly
between 30°C and 60°C, and the solvent is then
evaporated. The residue of the (indol-3-yl)glyoxylic
20 acid chloride which remains is dissolved or suspended
in an aprotic solvent, such as, for example,
tetrahydrofuran, dioxane, diethyl ether, toluene or
alternatively in a dipolar aprotic solvent, such as,
for example, dimethylformamide, dimethylacetamide or
25 dimethyl sulfoxide, cooled to a temperature between
-10°C and +10°C, preferably to -5°C to 0°C, and treated
with a solution of the primary or secondary amine in a
diluent in the presence of an acid scavenger. Possible
30 diluents are the solvents used for the dissolution of
the "indolyl-3-glyoxylic acid chloride". Acid
scavengers used are triethylamine, pyridin,
dimethylaminopyridine, basic ion exchanger, sodium
carbonate, potassium carbonate, powdered potassium
hydroxide and excess primary or secondary amine
35 employed for the reaction. The reaction takes place at
a temperature from 0°C to 120°C, preferably at
20 - 80°C, particularly between 40°C and 60°C. After a
reaction time of 1 - 4 hours and standing at room
temperature for 24 hours, the precipitate is digested

- with water, and the solid is filtered off with suction and dried in vacuo. The desired compound is purified by recrystallization in an organic solvent or by column chromatography on silica gel or alumina. The solvent used is, for example, a mixture of dichloromethane and ethanol (10:1, vol/vol).

2nd stage

- 10 The "indol-3-ylglyoxylamide" obtained according to the abovementioned 1st Stage procedure is dissolved in a protic, dipolar aprotic or nonpolar organic solvent, such as, for example, in isopropanol, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dioxane, toluene or methylene chloride and added dropwise to a suspension of a base such as, for example, sodium hydride, powdered potassium hydroxide, potassium tert-butoxide, dimethylaminopyridine or sodium amide in a suitable solvent, in a molar amount or in excess prepared in a 3-necked flask under an N_2 atmosphere. The desired alkyl, aralkyl or heteroaralkyl halide is then added either in undiluted form or in a diluent which was also used, for example, to dissolve the "indol-3-ylglyoxylamide", if appropriate with addition of a catalyst, such as, for example, copper, and the mixture is allowed to react for some time, e.g. 30 minutes to 12 hours, and the temperature is kept within a range between 0°C and 120°C, preferably between 30°C and 30 80°C, particularly between 50 and 70°C. After completion of the reaction, the reaction mixture is added to water, the solution is extracted, for example, with diethyl ether, dichloromethane, chloroform, methyl tert-butyl ether, tetrahydrofuran or N-butanol and the 35 organic phase obtained in each case is dried using anhydrous sodium sulfate.

The organic phase is concentrated in vacuo, the residue which remains is crystallized by trituration or the oily residue is purified by distillation or by column

chromatography or flash chromatography on silica gel or alumina. The eluent used is, for example, a mixture of methylene chloride and diethyl ether in the ratio 8:2 (vol/vol) or a mixture of methylene chloride and ethanol in the ratio 9:1 (v/v).

Working Examples

According to this general procedure for Stages 1 and 2, on which synthesis Scheme 2 is based, compounds were synthesized which have already been prepared according to the synthesis course of reaction Scheme 1 and are evident from Table 1. The relevant precursors of these compounds are evident from Table 2.

Example 27

N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl]-glvoxylamide

(Final substance, identical to Example 1)

1st stage

N-(Pyridin-4-yl)-(indol-3-yl)glvoxylamide

A solution of 10 g (85.3 mmol) of indole in 100 ml of ether is added dropwise at 0°C to a solution of 9 ml of oxalyl chloride in 100 ml of anhydrous ether. The mixture is kept under reflux for 3 hours. A suspension of 12 g (127.9 mmol) of 4-aminopyridine in 500 ml of tetrahydrofuran is then added dropwise at -5°C, and the reaction mixture is heated to reflux temperature with stirring for 3 hours and allowed to stand overnight at room temperature. The precipitate is filtered and treated with water and the dried compound is purified on a silica gel column (silica gel 60, Merck AG, Darmstadt) using the eluent methylene chloride/ethanol (10:1, v/v).

Yield: 9.8 g (43.3% of theory)

M.p.: from 250°C

5 2nd stage

N-(Pyridin-4-yl)-[1-[4-fluorobenzyl]indol-3-yl]glyoxylamide

10 The N-(pyridin-4-yl)-(indol-3-yl)glyoxylamide obtained according to the 1st stage is reacted with 4-fluorobenzyl chloride according to the "benzylation procedure" (Page 11) and the compound obtained is isolated.

15 Yield: 41% of theory

M.p.: 224-225°C

20 Elemental analysis:

Calc.	C 70.77	H 4.32	N 11.25
Found	C 70.98	H 4.40	N 11.49

Example 28 N-(4-Nitrophenyl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
25 (Final substance, identical to Example 7)

Example 29 N-(4-Fluorophenyl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
(Final substance, identical to Example 6)

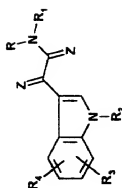
30 Example 30 N-(Pyridin-3-yl)-[1-(4-fluorobenzyl)-indol-3-yl]glyoxylamide
(Final substance, identical to Example 3)

35

The following precursors (1st stage of reaction scheme 2, Table 2) were obtained according to the present Scheme 2.

- | | | |
|----|------------|--|
| 5 | Example 31 | N-(Pyridin-4-yl)-(indol-3-yl)-
glyoxylamide |
| | Example 32 | N-(4-Nitrophenyl)-(indol-3-yl)-
glyoxylamide |
| | Example 33 | N-(4-Fluorophenyl)-(indol-3-yl)-
glyoxylamide |
| 10 | Example 34 | N-(Pyridin-3-yl)-(indol-3-yl)-
glyoxylamide |

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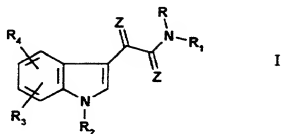
Formula 1

Example	R	R ₁	R ₂	R ₃	R ₄	Z	M.p.
Ex. 31	H		H	H	H	O	>260°C
Ex. 32	H		H	H	H	O	>250°C
Ex. 33	H		H	H	H	O	233.5°C
Ex. 34	H		H	H	H	O	235°C

Table 2: Novel indolylglyoxylamides according to reaction Scheme 2

Patent Claims

1. N-substituted indol-3-glyoxylamides of the formula
1

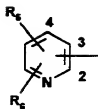


5

and their acid addition salts,
where the radicals R, R₁, R₂, R₃, R₄ and Z have the
following meaning:

- 10 R = hydrogen, (C₁-C₆)-alkyl, where the alkyl group can
be mono- or polysubstituted by the phenyl ring.
This phenyl ring, for its part, can be mono- or
polysubstituted by halogen, (C₁-C₆)-alkyl, (C₃-C₇)-
15 cycloalkyl, by carboxyl groups, carboxyl groups
esterified with (C₁-C₆)-alkanols, trifluoromethyl
groups, hydroxyl groups, methoxy groups, ethoxy
groups, benzyloxy groups and by a benyl [sic]
group which is mono- or polysubstituted in the
phenyl moiety by (C₁-C₆)-alkyl groups halogen atoms
20 or trifluoromethyl groups,

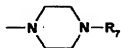
- R₁ can be a phenyl ring which is mono- or poly-
substituted by (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy,
hydroxyl, benzyloxy, nitro, amino, (C₁-C₆)-
25 alkylamino, (C₁-C₆)-alkoxy-carbonylamino and by a
carboxyl group or a carboxyl group esterified by
(C₁-C₆)-alkanols, or is a pyridin structure of the
formula II



Formula II

- where the pyridin structure is alternatively bonded to the ring carbon atoms 2, 3 and 4 and can be substituted by the substituents R_5 and R_6 . The radicals R_5 and R_6 can be identical or different and have the meaning (C_1-C_6) -alkyl, and also the meaning (C_3-C_7) -cycloalkyl, (C_1-C_6) -alkoxy, nitro, amino, hydroxyl, halogen and trifluoromethyl and are furthermore the ethoxy-carbonylamino radical and the group carboxy-alkyloxy in which the alkyl group can have 1-4 C atoms,
- R_1 can furthermore be a 2- or 4-pyrimidinyl-heterocycle or a pyridylmethyl radical in which CH_2 can be in the 2-, 3-, 4-position where the 2-pyrimidinyl ring can be mono- or polysubstituted by the methyl group, furthermore are [sic] the 2-, 3- and 4-quinolyl structure substituted by (C_1-C_6) -alkyl, halogen, the nitro group, the amino group and the (C_1-C_6) -alkylamino radical, or are [sic] a 2-, 3- and 4-quinolyl methyl group, where the ring carbons of the pyridylmethyl and quinolylmethyl radical can be substituted by (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, nitro, amino and (C_1-C_6) -alkoxy-carbonylamino,
- R_1 for the case where R is hydrogen or the benzyl group, can furthermore be the acid radical of a natural or unnatural amino acid, e.g. the α -glycyl, the α -sarcosyl, the α -alanyl, the α -leucyl, the α -isoleucyl, the α -seryl, the α -phenylalanyl, the α -histidyl, the α -prolyl, the

α -arginyl, the α -lysyl, the α -asparagyl and the α -glutamyl radical, where the amino groups of the respective amino acids can be present in unprotected or protected form and are possible protective groups for the amino function of the carbobenzoxy radical (Z radical) and the tert-butoxycarbonyl radical (BOC radical) and also the acetyl group. In the case of the asparagyl and glutamyl radical claimed for R_1 , the second, nonbonded carboxyl group is present as a free carboxyl group or in the form of an ester with C_1 - C_6 -alkanols, e.g. as the methyl, ethyl or as the tert-butyl ester. R_1 can furthermore be the allylaminocarbonyl-2-methylprop-1-yl group. R and R_1 , together with the nitrogen atom to which they are bonded, can furthermore form a piperazine ring of the formula III or a homopiperazine ring if R_1 is an aminoalkylene group in which



Formula III

R_1 is an alkyl radical, a phenyl ring which can be mono- or polysubstituted by (C_1 - C_6)-alkyl, (C_1 - C_6)-alkoxy, halogen, the nitro group, the amino function, by (C_1 - C_6)-alkylamino, the benzhydryl group and the bis-p-fluorobenzylhydriyl group,

R_2 can be hydrogen or the (C_1 - C_6)-alkyl group, where the alkyl group can be mono- or polysubstituted by halogen and phenyl which for its part can be mono- or polysubstituted by halogen, (C_1 - C_6)-alkyl, (C_3 - C_7)-cycloalkyl, carboxyl groups, carboxyl groups esterified with (C_1 - C_6)-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups. The (C_1 - C_6)-alkyl group counting as R_2 can furthermore be substituted by the 2-quinolyl group and the 2-, 3- and 4-pyridyl

structure, which in each case can both be mono- or polysubstituted by halogen, (C₁-C₄)-alkyl groups or (C₁-C₄)-alkoxy groups. R₂ is furthermore the aroyl radical, where the aryl moiety on which this radical is based is the phenyl ring which can be mono- or polysubstituted by halogen, (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, carboxyl groups, carboxyl groups esterified by (C₁-C₆)-alkanols, trifluoromethyl groups, hydroxyl groups, methoxy groups, ethoxy groups or benzyloxy groups,

R₃ and R₄ can be identical or different and are hydrogen, hydroxyl, (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, (C₁-C₆)-alkanoyl, (C₁-C₆)-alkoxy, halogen and benzyloxy. R₃ and R₄ can furthermore be the nitro group, the amino group, the (C₁-C₄)-mono- or dialkyl-substituted amino group, and the (C₁-C₃)-alkoxycarbonylamino function or the (C₁-C₃)-alkoxy-carbonylamino- (C₁-C₃)-alkyl function,

Z is O or S,

and where the designation alkyl, alcohol, alkoxy or alkylamino group for the radicals R, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ is normally to be understood as meaning "straight-chain" and "branched" alkyl groups, where "straight-chain alkyl groups" can be, for example, radicals such as methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl and "branched alkyl groups" designate, for example, radicals such as isopropyl or tert-butyl. "Cycloalkyl" is to be understood as meaning radicals such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, additionally the designation "halogen" represents fluorine, chlorine, bromine or iodine, and the designation "alkoxy group" represents radicals such as, for example, methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or pentoxy.

2. Compounds according to Claim 1

N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl]-
glyoxylamide

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N-(Pyridin-4-yl)-(4-methylindol-3-yl)glyoxylamide

N-(Pyridin-3-yl)-[1-(4-fluorobenzyl)-indol-3-yl]-
glyoxylamide

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N-(Pyridin-3-yl)-(1-benzylindol-3-yl)glyoxylamide

N-(Pyridin-3-yl)-[1-(2-chlorobenzyl)indol-3-yl]-
glyoxylamide

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N-(4-Fluorophenyl)-[1-(4-fluorobenzyl)indol-3-yl]-
glyoxylamide

N-(4-Nitrophenyl)-[1-(4-fluorobenzyl)indol-3-yl]-
glyoxylamide

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N-(2-Chloropyridine-3-yl)-[1-(4-fluorobenzyl)indol-3-
yl]glyoxylamide

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N-(Pyridin-4-yl)-(-benzylindol-3-yl)glyoxylamide

N-(Pyridin-4-yl)-[1-(3-pyridylmethyl)indol-3-yl]-
glyoxylamide

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N-(4-Fluorophenyl)-[1-(2-pyridylmethyl)indol-3-yl]-
glyoxyamide

N-(4-Fluorophenyl)-[1-(3-pyridylmethyl)indol-3-yl]-
glyoxylamide

35

N-(Pyridin-4-yl)-[1-(4-chlorobenzyl)indol-3-yl]-
glyoxylamide

N-(Pyridin-4-yl)-[1-(2-chlorobenzyl)indol-3-yl]-glyoxylamide

5 N-(Pyridin-2-yl)-[1-(4-fluorobenzyl)indol-3-yl]-glyoxylamide

N-(Pyridin-4-yl)-[1-(2-pyridylmethyl)indol-3-yl]-glyoxylamide

10 (4-Phenylpiperazin-1-yl)-[1-(4-fluorobenzyl)indol-3-yl]-glyoxylamide

N-(Pyridin-2-yl)-(1-benzylindol-3-yl)glyoxylamide

15 4-(Pyridin-4-yl)-piperazin-1-yl)-[1-(4-fluorobenzyl)indol-3-yl]glyoxylamide

N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-6-ethoxycarbonylaminoindol-3-yl]glyoxylamide

20 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-5-ethoxycarbonylaminoindol-3-yl]glyoxylamide

25 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-6-cyclopentyl-oxycarbonylaminoindol-3-yl]glyoxylamide

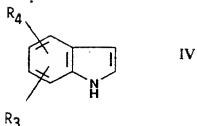
N-(3,4,5-Trimethoxybenzyl)-N-(allylaminocarbonyl-2-methylprop-1-yl)-[1-(4-fluorobenzyl)indol-3-yl]-glyoxylamide

30 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-5-methoxyindol-3-yl]glyoxylamide

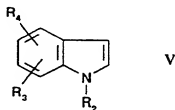
35 N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-5-hydroxyindol-3-yl]glyoxylamide

N-(Pyridin-4-yl)-[1-(4-fluorobenzyl)-5-ethoxycarbonylaminomethylindol-3-yl]glyoxylamide

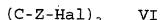
3. Use of the compounds of the formula I according to one of claims 1 and 2 for the production of a medicament.
- 5 4. Use of the compounds of the formula I according to claims 1 to 3 on their own or in combination with one another for the production of a medicament having antiasthmatic, antiallergic and immuno-suppressant/immunomodulating action for transplantation and diseases such as, for example, psoriasis, 10 rheumatoid disorders and chronic polyarthritis.
5. Medicaments comprising at least one compound of the formula I according to one of claims 1 and 2 in 15 addition to customary excipients and/or diluents or auxiliaries.
6. Process for the production of a medicament, characterized in that a compound of the formula I 20 according to one of claims 1 and 2 is processed with customary pharmaceutical excipients and/or diluents or other auxiliaries to give pharmaceutical preparations or brought into a therapeutically useable form.
- 25 7. Medicaments according to claims 1 to 6 in the form of tablets, coated tablets, capsules, solutions or ampoules, suppositories, patches, powder preparations which can be employed by inhalation, suspensions, creams and ointments.
- 30 8. Process for the preparation of N-substituted indole-3-glyoxylamides of the formula I according to claims 1 and 2, in which R, R₁, R₂, R₃, R₄ and Z have the meaning mentioned in claim 1, characterized in that 35 a) an indole derivative of the formula IV



- in which R_3 and R_4 have the meaning mentioned, is added to a suspended base in a protic, dipolar aprotic or nonpolar organic solvent, reacted with a reactive compound which carries the radical R_2 and where R_2 has the meaning mentioned, the 1-indole derivative of the formula V



- in which R_2 , R_3 and R_4 have the meaning mentioned, is reacted with a reactive compound of the formula VI



- in which Z has the meaning oxygen and Hal is a halogen fluorine, chlorine, bromine or iodine, and then with a primary or secondary amine of the formula VII

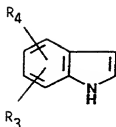


- in which R and R_1 have the meaning mentioned, in an aprotic or dipolar aprotic solvent and the target compound of the formula I is isolated,

or

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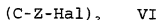
- b) an indole derivative of the formula IV



IV

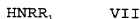
in which R_3 and R_4 have the meaning mentioned, is reacted in an aprotic or nonpolar solvent with a reactive compound of the formula VI

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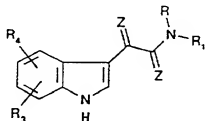
in which Z has the meaning oxygen and Hal is a halogen fluorine, chlorine, bromine or iodine, and then in an aprotic or dipolar aprotic solvent with a primary or secondary amine of the formula VII

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in which R and R_1 have the meaning mentioned, and then the 3-indole derivative of the formula VIII

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VIII

in which R, R_1 , R_2 , R_3 , R_4 and Z have the meaning mentioned, is reacted in a protic, dipolar aprotic or nonpolar organic solvent in the presence of a suspended base with a reactive compound which carries the radical R_2 and where R_2 has the meaning mentioned, and the target compound of the formula I is isolated.

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Abstract

The invention relates to novel N-substituted indole-3-glyoxyamides, to processes for their preparation and to their pharmaceutical use. The compounds have antiasthmatic, antiallergic and immuno-suppressant/immunomodulating actions.